



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US87/02530 (22) International Filing Date: 2 October 1987 (02.10.87) (31) Priority Application Numbers: 919,358 025,118 (32) Priority Dates: 16 October 1986 (16.10.86) 12 March 1987 (12.03.87) (33) Priority Country: US (71) Applicant: AMERICAN HEALTH PRODUCTS CORPORATION [US/US]; S.E. Financial Center, Suite 4370, 200 South Biscayne Boulevard, Miami, FL 33131 (US). (72) Inventors: FROST, Phillip ; 125 East San Marino Drive, Miami Beach, FL 33139 (US). HSIAO, Charles, H. ; 4890 S.W. 104th Avenue, Cooper City, FL 33328 (US).		(74) Agent: WEGNER, Harold, C.; Wegner & Bretschneider, P.O. Box 18218, Washington, DC 20036-8218 (US). (81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: 2',3'-DIDESOXYADENOSINE COMPOSITION (57) Abstract A pharmaceutical composition for the oral treatment of acquired immune deficiency syndrome which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine.		

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2' 3'-DIDESOXYADENOSINE COMPOSITIONBACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions
5 useful in the oral treatment of Acquired Immune Deficiency Syndrome.

2',3'-didesoxyadenosine is a known compound. Methacrylates are known as coatings for pharmaceuticals, including Eudragit polymers of Rohm
10 Pharma. Hydroxypropylmethylcellulose is known as a sustained release matrix, as disclosed first by Christenson et al., U.S. Patent 3,065,143 and again by Schor et al., U.S. Patent 4,389,393.

DESCRIPTION OF THE INVENTION

15 In accordance with a first aspect of the present invention there is provided a pharmaceutical composition for the treatment of acquired immune deficiency syndrome which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-
20 didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine.
25 Acquired immune deficiency syndrome was found by a prior researcher to be treated in vitro, but not in vivo, with 2',3'-didesoxyadenosine. According to the present invention, the 2',3'-didesoxyadenosine is permitted to remain free of degradation that apparently takes place in
30 the stomach fluids by blocking contact of the 2',3'-didesoxyadenosine with the stomach fluids through said outer pharmaceutically inert component stable in acidic pH.

In a preferred aspect, there is provided a plurality of dosage subunits each having at least three components

including a component of 2',3'-didesoxyadenosine sandwiched between pharmaceutically inert layers, at least the outer one of which is stable in acidic pH and which dissolves in a basic pH, whereby upon oral administration of said
5 pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine. As an inner layer remote from the gastrointestinal fluids may be mentioned a nonpareil seed.

In a still further embodiment of this aspect of the
10 invention there is provided a capsule containing said plurality of dosage subunits. As an alternative embodiment, there is provided a compressed tablet containing said plurality of dosage subunits, the matrix of said tablet disintegrating in the gastrointestinal tract to
15 yield said plurality of dosage subunits.

In accordance with a second aspect of the present invention there is provided a pharmaceutical composition for the oral treatment of acquired immune deficiency syndrome which comprises a component of 2',3'-
20 didesoxyadenosine and a barrier component to shield the 2',3'-didesoxyadenosine from the gastrointestinal fluids until said pharmaceutical composition passes into the small intestine, said barrier component being substantially impervious to degradation in a fluid other than a basic
25 medium, whereby upon introduction into the gastrointestinal tract beyond the stomach said 2',3'-didesoxyadenosine is released.

In a third aspect of the present invention there is provided a sustained release composition for the
30 introduction of 2',3'-didesoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-

didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine, said dosage subunits releasing said 2',3'-didesoxyadenosine only over a prolonged period of time.

In accordance with this third aspect of the present invention there is provided a sustained release composition for the introduction of 2',3'-didesoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which only erodes in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine, at least some of said dosage subunits including an outer core of a slowly erodible polymeric material, whereby a sustained release of 2',3'-didesoxyadenosine is achieved.

In an alternate embodiment, there is provided a sustained release composition for the introduction of 2',3'-didesoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine, said dosage subunits

being contained in a matrix of a polymer which only gradually exposes said dosage subunits to the environment of the gastrointestinal tract. In one embodiment, the polymer is a hydroxypropylmethylcellulose, with a tablet
5 made up of from about 60 to 95 percent, and preferably 80 to 92 percent by weight of said dosage subunits and from about 5 to about 40 percent, and preferably from about 8 to about 20 percent of the hydroxypropylmethyl-cellulose. As a hydroxypropylmethylcellulose suitable for the present
10 invention may be mentioned Methocel K15M (Dow Chemical Co., Midland, Michigan) and Methocel K4M (Dow Chemical Co., Midland, Michigan).

A total adult daily dosage which is spread out over three to five administrations per day, or twice daily in the
15 sustained release aspect of the present invention, comprises from about 2 to about 1000 mg per day, preferably about 25 to about 750 mg per day, and still more preferably about 10 to 250 mg per administration.

EXAMPLE I

20 Nonpareil seeds (20 to 30 mesh) are wetted with polyvinylpyrrolidone solution using Kollidon 30 (BASF, mw 30,000) which has been first dissolved in isopropanol in a coating pan with repeated dustings of 2',3'-didesoxyadenosine (about ten to twenty times) to build up a
25 2',3'-didesoxyadenosine-coated nonpareil seed.

EXAMPLE II

Alcohol dissolved Kollidone 90 (BASF, mw 90,000) is used as a wetting agent for nonpareil seeds (20 to 30 mesh) in a coating pan with repeated dustings of 2',3'-
30 didesoxyadenosine (about ten to twenty times) to build up a 2',3'-didesoxyadenosine-coated nonpareil seed.

EXAMPLE III

The 2',3'-didesoxyadenosine-coated nonpareil seeds of Example I are introduced into a Wurster column (Glatt) and

coated with a methylmethacrylate in a solvent, using 50 gm Eudrigit L (Rohm Pharma) in a solvent mixture of 250 cc acetone and 250 cc isopropanol. After coating in the Wurster column, the total weight of 2',3'-didesoxyadenosine as a percentage of 2',3'-didesoxyadenosine plus coating is 45%. The dosage subunits dissolve readily in the small intestine.

EXAMPLE IV

2',3'-Didesoxyadenosine-coated nonpareil seeds of Example I are introduced into a Wurster column (Glatt) and coated with a methylmethacrylate in a solvent, using 25 gm Eudrigit L (Rohm Pharma), 25 gm Eudragit RS (Rohm Pharma) in a solvent mixture of 250 cc acetone and 250 cc isopropanol. After coating in the Wurster column, the total weight of 2',3'-didesoxyadenosine as a percentage of 2',3'-didesoxyadenosine plus coating is 45%. The inclusion of the Eudrigit RS retards dissolution of the dosage subunits to permit a sustained delivery of the 2',3'-didesoxyadenosine into the bloodstream of the patient.

EXAMPLE V

Capsules are made of a plurality of dosage subunits of Example III to make up 250 mg 2',3'-didesoxyadenosine per capsule. The capsules dissolve in the gastrointestinal tract upon oral administration, and each of the dosage subunits releases 2',3'-didesoxyadenosine in the small intestine, to provide 2',3'-didesoxyadenosine to the bloodstream.

EXAMPLE VI

Sustained release capsules are made of a plurality of dosage subunits of Example IV to make up 250 mg 2',3'-didesoxyadenosine per capsule. The capsules dissolve in the gastrointestinal tract upon oral administration, and each of the dosage subunits releases 2',3'-didesoxyadenosine in the small intestine, to provide 2',3'-

didesoxyadenosine to the bloodstream of the subject.

EXAMPLE VII

Tablets of a total weight of 330 mg are produced by mixing and then compressing together in a ratio of 10:1 of
5 the dosage subunits of Example II and hydroxypropylmethylcellulose (Methocel K15M, Dow Chemical Co., Midland Michigan).

The sustained release tablet of this example provides an advantage over the other dosage forms in that the dosage
10 subunits are only gradually exposed to the environment of the gastrointestinal fluids, whereby 2',3'-didesoxyadenosine is introduced into the bloodstream over a prolonged period of time.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for the oral treatment of acquired immune deficiency syndrome which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine.
2. A pharmaceutical composition of claim 1 for the oral treatment of acquired immune deficiency syndrome which comprises a plurality of dosage subunits each having at least three components including a component of 2',3'-didesoxyadenosine sandwiched between pharmaceutically inert layers, at least the outer one of which is stable in acidic pH and which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine.
3. A 2',3'-didesoxyadenosine pharmaceutical composition of claim 1 for the oral treatment of acquired immune deficiency syndrome which is a capsule containing said plurality of dosage subunits.
4. A pharmaceutical composition of claim 1 which is a compressed tablet containing said plurality of dosage subunits, the matrix of said tablet disintegrating in the gastrointestinal tract to yield said plurality of dosage subunits.
5. A pharmaceutical composition for the oral treatment of acquired immune deficiency syndrome which comprises a component of 2',3'-didesoxyadenosine and a barrier component to shield the 2',3'-didesoxyadenosine from the gastrointestinal fluids until said pharmaceutical

composition passes into the small intestine, said barrier component being substantially impervious to degradation in a fluid other than a basic medium, whereby upon introduction into the gastrointestinal tract beyond the stomach said 2',3'-didesoxyadenosine is released.

6. A sustained release composition for the introduction of 2',3'-didesoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine, said dosage subunits releasing said 2',3'-didesoxyadenosine only over a prolonged period of time.

7. A sustained release composition for the introduction of 2',3'-didesoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which only erodes in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine, at least some of said dosage subunits including an outer core of a slowly erodible polymeric material, whereby a sustained release of 2',3'-didesoxyadenosine is achieved.




8. A sustained release composition for the introduction

of 2',3'-dideoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two
5 components including a component of 2',3'-dideoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-dideoxyadenosine is not exposed to gastrointestinal
10 fluids until the small intestine, said dosage subunits being contained in a matrix of a polymer which only gradually exposes said dosage subunits to the environment of the gastrointestinal tract.

9. A sustained release composition of claim 8 wherein
15 said polymer is a hydroxypropylmethylcellulose.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/02530

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ : A 61 K 31/70; A 61 K 9/54; A 61 K 9/22																	
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; padding: 5px;">IPC⁴</td> <td style="border: 1px solid black; padding: 5px;">A 61 K; C 07 H</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	IPC ⁴	A 61 K; C 07 H											
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border-bottom: 1px solid black;">Category ⁹</th> <th style="border-bottom: 1px solid black;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 10%; border-bottom: 1px solid black;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="border: 1px solid black; padding: 5px; vertical-align: top;">P,X</td> <td style="border: 1px solid black; padding: 5px;">EP, A, 0206497 (THE WELLCOME FOUNDATION LTD) 30 December 1986, see page 1, lines 1-26; page 4, ligne 23; page 6, lines 11-32; page 12, formulation F; page 13, formulation E --</td> <td style="border: 1px solid black; padding: 5px; text-align: center; vertical-align: top;">1-9</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px; vertical-align: top;">Y</td> <td style="border: 1px solid black; padding: 5px;">Chemical Abstracts, volume 104, no. 21, 26 May 1986, (Columbus, Ohio, US), H. Mitsuya et al.: "Inhibition of the in vitro infectivity and cytophatic effect of human T-lymphotrophic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxy-nucleosides", see page 352, abstract 183216h, & Proc. Natl. Acad. Sci. U.S.A. 1986, 83(6), 1911-15 --</td> <td style="border: 1px solid black; padding: 5px; text-align: center; vertical-align: top;">1-9</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px; vertical-align: top;">Y</td> <td style="border: 1px solid black; padding: 5px;">EP, A, 0136464 (BIOSEARCH S.p.A.) 10 April 1985, see pages 1,2; page 13, line 9 - page 15, line 20; claims --</td> <td style="border: 1px solid black; padding: 5px; text-align: center; vertical-align: top;">1-9</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px; vertical-align: top;">Y</td> <td style="border: 1px solid black; padding: 5px;">EP, A, 0032562 (Dr Karl THOMAE GmbH) 29 July 1981, see pages 21,22; examples ./. ./.</td> <td style="border: 1px solid black; padding: 5px; text-align: center; vertical-align: top;">1-8</td> </tr> </table>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	P,X	EP, A, 0206497 (THE WELLCOME FOUNDATION LTD) 30 December 1986, see page 1, lines 1-26; page 4, ligne 23; page 6, lines 11-32; page 12, formulation F; page 13, formulation E --	1-9	Y	Chemical Abstracts, volume 104, no. 21, 26 May 1986, (Columbus, Ohio, US), H. Mitsuya et al.: "Inhibition of the in vitro infectivity and cytophatic effect of human T-lymphotrophic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxy-nucleosides", see page 352, abstract 183216h, & Proc. Natl. Acad. Sci. U.S.A. 1986, 83(6), 1911-15 --	1-9	Y	EP, A, 0136464 (BIOSEARCH S.p.A.) 10 April 1985, see pages 1,2; page 13, line 9 - page 15, line 20; claims --	1-9	Y	EP, A, 0032562 (Dr Karl THOMAE GmbH) 29 July 1981, see pages 21,22; examples ./. ./.	1-8
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Δ" document member of the same patent family</p> </div> </div>																	
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">Date of the Actual Completion of the International Search</td> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">Date of Mailing of this International Search Report</td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px; text-align: center;">20th January 1988</td> <td style="border-bottom: 1px solid black; padding: 5px; text-align: center;">19 FEB 1988</td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px;">International Searching Authority</td> <td style="border-bottom: 1px solid black; padding: 5px;">Signature of Authorized Officer</td> </tr> <tr> <td style="padding: 5px; text-align: center;">EUROPEAN PATENT OFFICE</td> <td style="padding: 5px; text-align: center;">  P.C.G. VAN DER PUTTEN </td> </tr> </table>			Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	20th January 1988	19 FEB 1988	International Searching Authority	Signature of Authorized Officer	EUROPEAN PATENT OFFICE	 P.C.G. VAN DER PUTTEN							
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EUROPEAN PATENT OFFICE	 P.C.G. VAN DER PUTTEN																

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
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	6, A), B), C), D); page 24, example 9; page 25, example 10; claims 1,5,8,9, 11,12	
Y	-- WO, A, 84/02843 (EGYT GYOGYSZERVEGYESZETI GYAR) 2 August 1984, see the abstract	8,9

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

US 8702530

SA 19151

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 05/02/88. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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